MAGNETIC RESONANCE IN CHEMISTRY, VOL. 35, 13–20 (1997)

Chemical Shift Assignment of Geminal Protons in 3,7-Diazabicyclo[3.3.1]nonanes: An Unexpected Deviation from the Axial/Equatorial Chemical Shift Order

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The chemical shift order of axial and equatorial methylene protons in 1,5-disubstituted 3,7-diazabicyclo[3.3.1]nonan-9-ones may be altered by substituents in the 1,5-positions, but the corresponding alcohols behave differently. Unambiguous signal assignments for a series of the title compounds are provided, based on $^3J_{CH}$ coupling constants and on {^{1}H} ^{13}C heteronuclear Overhauser effects. Substituent anisotropy effects as a source of the chemical shift changes are discussed.

Magn. Reson. Chem. **35**, 13–20 (1997) No. of Figures: 8 No. of Tables: 6 No. of References: 23

Keywords: NMR; ^{1}H NMR; ^{13}C NMR; 3,7-diazabicyclo[3.3.1]nonane; heteronuclear Overhauser effect; HSBC; 2D heteronuclear correlation

Received 19 February 1996; revised 15 August 1996; accepted 19 August 1996

INTRODUCTION

One of the most applicable rules for the assignment of proton NMR spectra concerns the relative chemical shift order of axial and equatorial protons in cyclohexane derivatives and their element analogues.[1] It is usually observed that the chemical shift difference for protons in the cyclohexane chair conformation, $\Delta\delta_{eq,\,ax} = \delta_{eq} - \delta_{ax}$, is positive, owing to the anisotropy of the C—C single bonds. Exceptions can be observed in the presence of magnetically anisotropic substituents.[2] We report here the complete signal assignments for a series of 3,7-diazabicyclo[3.3.1]nonane (bispidine) derivatives, including a deviation from this rule.

RESULTS AND DISCUSSION

Bispidine derivatives are of interest as pharmacologically active compounds[3] and as rigid cyclohexane models,[4] and have recently gained new interest as metal ion scavengers.[5] Current work in our laboratory is aimed at their use as ligands in palladium complexes.[6] In the course of this work, we have prepared a series of 1,5-dicarboxymethyl bispidinones (**1**) (Scheme 1). The methylene proton signals of these compounds appear as pairs of AB doublets. Owing to the substitution pattern, no vicinal coupling constants are available to distinguish axial and equatorial methylene protons. In view of the considerable interest in 3,7-diazabicyclo[3.3.1]nonane derivatives and their element analogues, it is surprising that a sound assignment of these protons has rarely been attempted. With few exceptions, reported assignments of proton spectra are either based on empirical rules for cyclohexane derivatives,[5b,c] or they are done without any explanation at all, or signals are unassigned or not listed.[4b,7] However, an unequivocal assignment is possible based on (i) the heteronuclear vicinal coupling constant ($^3J_{CH}$) between the methylene protons, i.e. H_{ax} or H_{eq} and the keto or the ester carbonyl carbons and (ii) the heteronuclear Overhauser effect from these protons to the same carbons.

Bispidine derivatives can be involved in conformational equilibria (Fig. 1), which in simple cases are revealed by the number of ^{13}C NMR signals.[8b] If the nitrogens are unsubstituted (R_2 = H) or have electron-withdrawing substituents, the twin chair (CC) conformation, possibly flattened, is preferred.[8,9b] The boat–chair (BC) conformation has been reported for compounds with substituent R_2 in an *endo* position,[9] or with large substituents on the ring carbons C-2, C-4, C-6 and C-8.[8b,c,9] The degenerate equilibrium CB $\rightleftharpoons$ BC has a $\Delta G^{\ddagger}$ between 35 and 40.6 kJ mol^{-1}, depending on the nitrogen substituents.[8b,10] BB conformers have not been reported so far.[8a,c] Although we did not find any indication for conformers other than CC, even at low temperatures, initially we cannot completely rule out fast equilibria with low energy barriers. Therefore, we consider the two possibilities for the methylene proton arrangement shown in Fig. 2.

In the chair (of CC or BC conformer), H_{ax} and H_{eq} would have different angles with the carbonyl carbon

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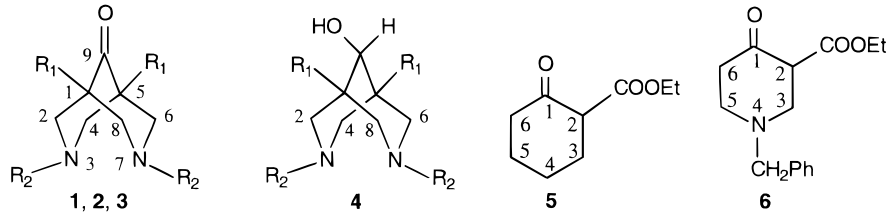
Contract grant sponsor: Swedish Natural Science Research Council.
Contract grant sponsor: Magn. Bergvalls Stiftelse.

CCC 0749–1581/97/010013–08



	R_1	R_2		R_1	R_2
1a	CO_2Me	CH_2Ph	**3a**	Ph	CH_2Ph
1b	CO_2Me	Ph	**3b**	Ph	H
1c	CO_2Me	$-CH_2-$	**4a**	CO_2Me	CH_2Ph
2a	Me	CH_2Ph	**4b**	CO_2Me	Ph
2b	Me	Ph	**4c**	Me	CH_2Ph
2c	Me	H	**4d**	Me	Ph

Scheme 1.

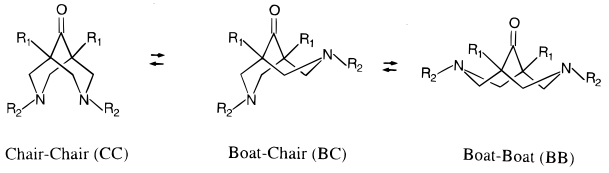


Figure 1. Conformational equilibria of bispidinone derivatives.

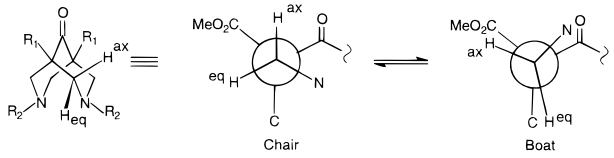


Figure 2. Newman projection along the C-1—C-2 bond for chair and boat conformers of the bispidinones.

(C-9). Molecular modelling yields dihedral angles between 170° and 180° for the equatorial proton and between 61° and 71° for the axial proton, in agreement with a reported x-ray crystallographic investigation of a related bispidine derivative[11] (Table 1). These angles correspond to $^3J_{CH}$ of 9 Hz (H_{eq}) and 1–2 Hz (H_{ax}), as estimated from a Karplus equation:[12]

$$^3J_{CH} = 4.50 - 0.87 \cos\theta + 4.03 \cos\theta \qquad (1)$$

Since we have no substituent corrections, the match between calculated and observed coupling constants is not perfect, but a distinction of H_{ax} and H_{eq} is possible. On the other hand, in the ring with a boat conformation of the BC conformer, the coupling constants for H_{ax} and H_{eq} with the carbonyl carbon (C-9) would not differ very much from each other (Table 1). Dihedral angles between the methylene protons and the carbon attached to C-1 or C-5 (e.g. the carboxy carbon) are expected to be similar for H_{ax} and H_{eq} in the CC conformer, whereas in the BC conformer, H_{ax} should have a larger coupling to these carbons than H_{eq}. Coupling constants were measured from cross peaks in HSBC (*H*eteronuclear *S*ingle quantum multiple *B*ond *C*orrelation) spectra[13] (Figs 3 and 4 and Table 2). These cross peaks contain the active, long-range heteronuclear coupling constant as an antiphase splitting along f_2. The coupling constant was determined from f_2 traces with *J*-doubling.[14]

Inspection of the HSBC spectrum of **3a** shows a pronounced cross peak between the methylene proton at lower chemical shift, previously assigned as H_{ax} by its chemical shift and the *ipso* carbon of the phenyl substituent. The methylene proton at higher chemical shift has instead a cross peak with the keto carbonyl carbon (Fig. 3), confirming the previous assignments based on $\Delta\delta_{eq,ax}$.[5b] However, in the carboxymethyl compounds **1a–c** the picture is reversed. The cross peaks now indicate that the equatorial proton is the one at lower chemical shift (Fig. 4). For **1c**, which has a fixed confor-

Table 1. Molecular geometry and calculated coupling constants in bispidinone derivatives

			Dihedral angles (°) and J_{CH} (Hz)[a]				Distances (Å)			
	R_1	R_2	H_{ax}-C-9	H_{ax}-R_1 [b]	H_{eq}-C-9	H_{eq}-R_1 [b]	H_{ax}-C-9	H_{ax}-R_1 [b]	H_{eq}-C-9	H_{eq}-R_1 [b]
N,N'-Diphenylbispidine[c]	H	Ph	69.0°	49.5°	174.0°	67.5°	2.82	2.37	3.45	2.48
J_{CH} =			1.2	(J_{HH} = 4.1)	9.3	1.9				
1b, CC[d]	CO_2Me	Ph	71.0°	51.0°	171.4°	66.6°	2.77	2.64	3.43	2.78
J_{CH} =			1.0	3.1	9.2	1.4				
1b, BC[d]	CO_2Me	Ph	124.9°	5.6°	119.2°	121.6°	3.29	2.56	3.23	3.29
J_{CH} =			3.6	7.6	2.8	3.1				

[a] Calculated coupling constants $^3J_{CH}$ [Eqn (1)] for the indicated dihedral angles.
[b] Angle or distance to the first atom of the substituent R_1.
[c] From x-ray crystallography.[11]
[d] Conformation: CC = chair–chair, BC = boat–chair; values are for the respective ring conformation. Conformations were optimized with molecular modelling (MM + parameter set[16]).

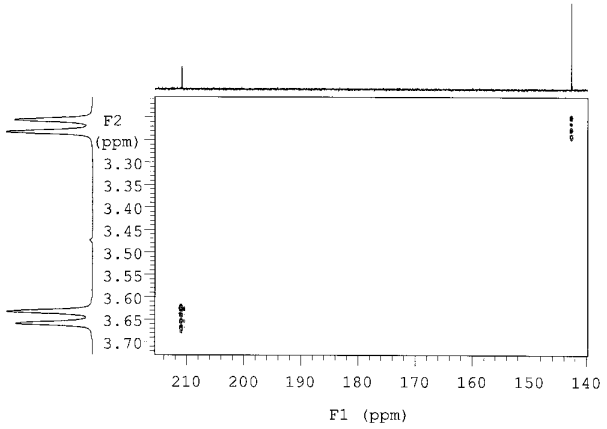


Figure 3. Expansion of the HSBC spectrum of **3a** showing correlation through $^3J_{CH}$ to the carbonyl and the *ipso*-phenyl carbons from $H_{2,\,4\text{-ax}}$ and $H_{2,\,4\text{-eq}}$.

mation, a pronounced cross peak is observed between H_{ax} and N—CH_2—N, whereas H_{eq} only has a weak cross peak with this carbon, in agreement with the dihedral angles between the atoms involved.

The inaccuracy of the calculated $^3J_{CH}$ values prevents a quantitative estimation of BC conformers, but the similarity of **1c** with both **1a** and **1b** indicates that their contribution must be small.

Additional and independent confirmation for the proton assignments is provided by heteronuclear Overhauser effects from the protons to keto carbons (C-9) and the carbons attached to C-1 and C-5 (i.e. carboxyl,

Table 2. Vicinal C–H coupling constants[a] $^3J_{CH}$ and heteronuclear Overhauser effect data for various bispidine derivatives

Compound	δ H	δ C	$^3J_{CH}$ (Hz)	NOE[c]	Proton assignment
1a	3.28	203.6	3.1	+	ax
		170.6	4.5	+	
	3.15	203.6	4.7	−	eq
		170.6	3.2	+	
1b	4.13	201.7	4.6	+	ax
		170.6	4.7	+	
	3.91	201.7	5.5	−	eq
		170.6	4.6	+	
1c	3.70	200.3	3.7		ax
		72.4	6.3		
	3.60	200.3	6.1		eq
		72.4	2		
2a	3.04	215.0	7.5		eq
		20.0	n.d.[b]		
	2.38	215.0	n.d.[b]		ax
		20.0	4.8		
2b	3.93	214.0	5.8		eq
		18.3	n.d.[b]		
	3.18	214.0	n.d.[b]		ax
		18.3	5.1		
3a	3.65	210.9	7.2	−	eq
		142.6	6.6	−	
	3.22	210.9	4.6	+	ax
		142.6	7.3	+	

[a] Measured from HSBC traces with *J*-doubling ($CDCl_3$ solutions, 25 °C).
[b] Not detected.
[c] +, NOE detected; −, no NOE detected; no entry, not measured.

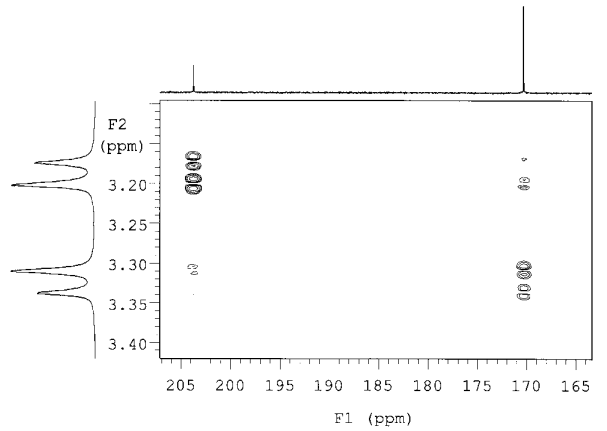


Figure 4. Expansion of the HSBC spectrum of **1a** showing correlation through $^3J_{CH}$ to the carbonyl and the carboxyl carbons from $H_{2,\,4\text{-ax}}$ and $H_{2,\,4\text{-eq}}$.

methyl or *ipso*-Ph). Based on the geometry of the CC conformers (Fig. 2), H_{ax} is expected to produce an equally large NOE for both C-9 and the carboxyl or *ipso*-Ph carbons, whereas H_{eq} should have an effect almost exclusively to the latter. This is confirmed by the experiment (Fig. 5 and Table 2). For the BC conformers, we would predict a strong effect from H_{ax} to the carboxyl (or *ipso*-Ph) carbon and no (or very weak) effects from any methylene proton to C-9. Since this was not the case, we conclude that the compounds occur predominantly if not exclusively in their CC conformation.

In the methyl derivatives **2**, it is more convenient to observe the homonuclear NOE from the methyl protons to H_{ax}, which is larger than the effect to H_{eq}, e.g. 6% *vs.* 2.5% for **2b**, which fits well to the chair–chair geometry.

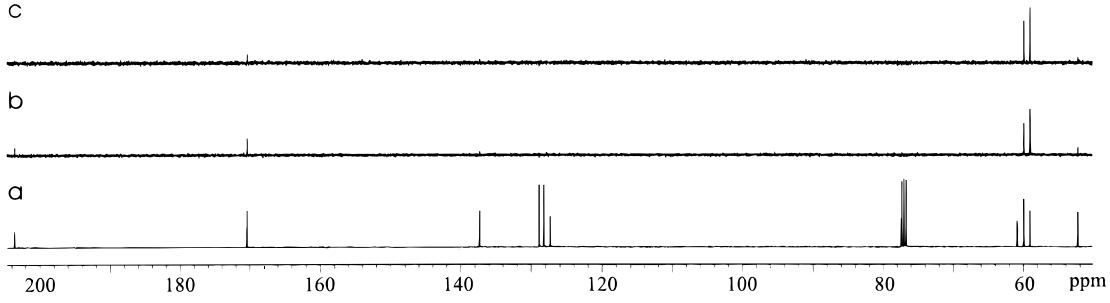


Figure 5. Heteronuclear NOE ($\{^1H\} \rightarrow {}^{13}C$) difference spectra for **1a**. (a) ^{13}C NMR reference spectrum; (b) saturation of proton signal at 3.28 ppm (c) saturation of proton signal at 3.15 ppm.

Table 3. ^{1}H and ^{13}C NMR data for the bispidine derivatives ($CDCl_3$ solution, 25 °C, 100–200 mg)

	1a		1b		1c		2a		2b		2c[a]	
	δ, ^{13}C	δ, ^{1}H	δ, ^{13}C	δ, ^{1}H	δ, ^{13}C	δ, ^{1}H	δ, ^{13}C	δ, ^{1}H	δ, ^{13}C	δ, ^{1}H	δ, ^{13}C	δ, ^{1}H
CO	203.4		201.7		200.3		215.0		214.0		215.4	
CO_2CH_3	170.2		169.6		168.8							
ipso	137.1		149.6				138.4		149.5			
ortho	128.7	7.31	129.0	7.01			128.7		115.4	6.81		
meta	128.1	7.31	120.9	7.27			128.2	7.32	129.0	7.18		
para	127.1	7.31	117.4	6.94			127.0		118.9	6.77		
$PhCH_2$	60.7	3.96			72.4[b]	4.05	61.3	3.53				
CH_2	59.7	3.28_{ax}	57.8	4.13_{ax}	60.7	3.70_{ax}	65.5	3.04_{eq}	62.3	3.93_{eq}	61.8	3.36_{eq}
		3.15_{eq}		3.91_{eq}		3.60_{eq}		2.38_{ax}		3.18_{ax}		2.95_{ax}
		$J = 11.1$		$J = 12.0$		$J = 12.8$ Hz		$J = 11.0$ Hz		$J = 12.2$ Hz		$J = 12.2$ Hz
CH_3O_2C	52.1	3.86	52.6	3.73	52.3	3.76						
C-1, C-5	58.9		59.0		55.9		46.7		47.0		49.4	
C-CH_3							20.0	0.96	18.3	1.16	17.2	0.88

	3a		4a		4b		4c	4d
	δ, ^{13}C	δ, ^{1}H		δ, ^{13}C	δ, ^{1}H		δ, ^{13}C	δ, ^{1}H	δ, ^{1}H	δ, ^{1}H
CO	210.9									
COO				173.8			173.5			
Ph-*ipso*	142.6		*ipso*-7	137.7		Ph-*ipso*	150.2, 149.6			
Bz-*ipso*	137.9		*ipso*-3	136.7		Ph-*meta*	129.0, 128.9	7.20	7.36	*meta*: 7.19
Bz-*ortho*	129.0	7.51	*meta*	128.3	7.19–7.38	Ph-*para*	119.4, 119.1	6.79		*para*: 6.72
Bz-*meta*	128.3	7.46	*ortho*	128.9, 128.7		Ph-*ortho*	115.8	6.92		*ortho*: 6.80
Ph-*meta*	127.7	7.36	*para*	127.32, 127.30						
Bz-*para*	127.4	7.38	*C*H(OH)	74.8	4.24	*C*H(OH)	70.9	4.62	2.86	3.33
Ph-*ortho*	126.8	7.29								
Ph-*para*	126.5	7.27								
			CH_3O	52.4	3.71	CH_3O	52.7	3.83	CH_3: 1.08	1.14
			C-6, C-8	59.6	2.61_{eq}	C-6, C-8	55.7	3.79_{eq}	2.50_{eq}	3.55_{eq}
					2.47_{ax}			3.33_{ax}	1.84_{ax}	2.75_{ax}
CH_2	64.8	3.65_{eq}	C-2, C-4	53.4	2.63_{eq}	C-2, C-4		3.63_{eq}	2.64_{eq}	3.30_{eq}
		3.22_{ax}			3.60_{ax}			3.75_{ax}	2.58_{ax}	3.12_{ax}
		$J = 10.5$								
$PhCH_2$	61.8	3.82	$PhCH_2$-7	61.24	3.50				$PhCH_2$-7: 3.50	
			$PhCH_2$-3	61.20	3.66				$PhCH_2$-3: 3.56	
C-1, C-5	54.4			49.2			48.1			
					OH: 5.13			OH: 3.46	OH: 4.57	OH: 2.02

[a] NH δ 2.67.
[b] N—CH_2—N.

Table 4. Comparison of methylene proton chemical shifts in structurally related bispidine derivatives ($R_1 = CH_3$ *vs.* $R_1 = COOCH_3$)

Compound	R_1	δ H_{ax}	δ H_{eq}	$\Delta\delta H_{ax}$[a]	$\Delta\delta H_{eq}$[a]	$\Delta\delta_{eq,\,ax}$
2a	CH_3	2.38	3.04			0.66
1a	$COOCH_3$	3.28	3.15	0.90	0.11	−0.13
2b	CH_3	3.18	3.93			0.75
1b	$COOCH_3$	4.13	3.91	0.95	−0.02	−0.22
4c, C_2/C_4	CH_3	2.58	2.64			0.06
4a, C_2/C_4	$COOCH_3$	3.60	2.63	1.02	−0.01	−0.97
4c, C_6/C_8	CH_3	1.84	2.50			0.66
4a, C_6/C_8	$COOCH_3$	2.47	2.61	0.63	0.11	0.14
4d, C_2/C_4	CH_3	3.12	3.30			0.18
4b, C_2/C_4	$COOCH_3$	3.75	3.63	0.63	0.33	−0.12
4d, C_6/C_8	CH_3	2.75	3.55			0.80
4b, C_6/C_8	$COOCH_3$	3.33	3.79	0.58	0.24	0.46

[a] $\delta_{R_1=COOCH_3} - \delta_{R_1=CH_3}$.

Alcohols **4a–d** show the normal shift order, i.e. $\Delta\delta_{eq,\,ax} > 0$, except for the protons on the OH-side, i.e. C-2/C-4 of **4a** and **4b** (Tables 3 and 4). Here, the assignment of the axial protons H-6_{ax} and H-8_{ax} is based on their NOE with C*H*(OH). Because of the CC geometry of these molecules, the axial methylene protons also have a strong cross peak with C-2/C-4 in the HSBC spectrum, which is not observed for the equatorial protons H-6_{eq} and H-8_{eq}. Likewise, the axial protons H-2_{ax} and H-4_{ax} are revealed by their HSBC cross peak with C-6/C-8. In addition, all equatorial protons are having cross peaks to the other CH_2 carbon in the same ring, e.g. H-2_{eq} with C-4. The signals of C-2/4 are also identified by a cross peak with C*H*(OH).

Finally, it should be noted that the methylene proton signals in alcohols **4a–d** are not doublets as in the parent ketones. Instead, the protons of each piperidine ring give rise to an AA′BB′ pattern. Additional couplings into the other piperidine ring result in AA′BB′CC′DD′ spin systems (Fig. 6). Coupling constants were determined by spin simulation using full-lineshape iteration (simulations were performed with gNMR v. 3.6[15]). Resulting parameter sets are shown in Table 5.

Compounds **1** are β-keto esters, and an interesting question is whether the observed chemical shift order, i.e. $\Delta\delta_{eq,\,ax} < 0$, is related to the conformationally restricted bispidinone skeleton. Unexpectedly, relevant data on 2-carboalkoxycyclohexanones are scarce in the literature at best. We therefore investigated the keto-carboxylic acid esters **5** and **6**. A complete proton signal assignment for their keto isomers (Table 6) shows that indeed $\Delta\delta_{eq,\,ax} < 0$ for the methylene protons on C-3, but not for those on C-5. The similarity of **5** and **6** proves that the nitrogen atom is not important. Based on the appearance of the spectra, it is reasonable to assume the main conformer of **5** and **6** to be a flattened chair with H-2 in an axial position (Table 6). This is supported by a molecular modelling and conforma-

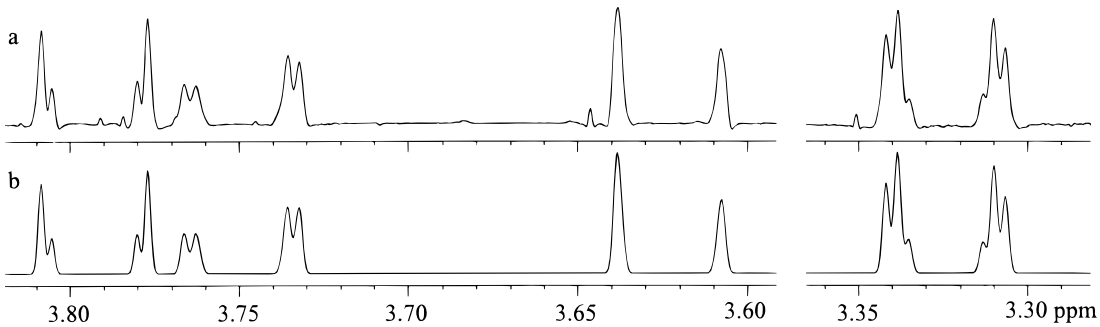


Figure 6. (a) Methylene proton signals of **4b** ($CDCl_3$ solution, 400 MHz, 25 °C). The FID was processed with Gaussian apodization prior to Fourier transformation. (b) Simulation of the signals with the parameters from Table 5, using a Gaussian lineshape.

Table 5. Spin simulation results for the methylene protons of alcohols 4a–d[a]

Compound	R_1	R_2	δH-2_{ax}	δH-2_{eq}	δH-4_{ax}	δH-4_{eq}	δH-6_{ax}	δH-6_{eq}	δH-8_{ax}	δH-8_{eq}	
4a	CO_2Me	Bz	3.597	2.627	3.597	2.627	2.467	2.608	2.467	2.608	
4b	CO_2Me	Ph	3.747	3.625	3.747	3.625	3.325	3.792	3.325	3.792	
4c	Me	Bz	2.581	2.636	2.581	2.636	1.840	2.499	1.840	2.499	
4d	Me	Ph	3.123	3.303	3.123	3.303	2.750	3.554	2.750	3.554	
			$J_{2eq,\,2ax}$	$J_{2eq,\,4eq}$	$J_{2ax,\,4eq}$	$J_{6eq,\,6ax}$	$J_{6eq,\,8eq}$	$J_{6eq,\,8ax}$	$J_{2ax,\,8ax}$	$J_{2eq,\,8eq}$	$J_{2eq,\,8ax}$
4a	CO_2Me	Bz	−11.28	1.00	−0.57	−10.76	1.60	−0.64	0.27	—	0.40
4b	CO_2Me	Ph	−12.10	0.43	−0.46	−12.03	1.16	−0.77	1.43	0.06	0.40
4c	Me	Bz	−10.59	0.80	−0.63	−10.89	1.86	−0.52	0.03	—	0.54
4d	Me	Ph	−11.67	0.54	−0.21	−11.84	1.25	−0.89	1.97	—	0.41

[a] Simulated for 400 MHz observation frequency with full-lineshape iteration of experimental spectra.[15] J in Hz. Further couplings: $J_{4eq,\,4ax} = J_{2eq,\,2ax}$, $J_{2eq,\,4ax} = J_{2ax,\,4eq}$, $J_{8eq,\,8ax} = J_{6ax,\,6eq}$, $J_{6eq,\,8ax} = J_{6ax,\,8eq}$, $J_{4ax,\,6ax} = J_{2ax,\,8ax}$, $J_{4eq,\,6eq} = J_{2eq,\,8eq}$, $J_{4eq,\,6ax} = J_{2eq,\,8ax}$.

Table 6. ^{1}H NMR data for the keto isomers of 5[a] (benzene-d_6 solution) and 6[b] (CDCl$_3$ solution)[c]

5	H-2	H-3$_{ax}$	H-3$_{eq}$	H-4$_{ax}$	H-4$_{eq}$
δ	3.05	1.95	1.66	1.00	1.33
J_{HH}(Hz)	$J_{2,3ax}$ = 10.3 $J_{2,3eq}$ = 5.6 $J_{2,6ax}$ = 1.3	$J_{3ax,eq}$ = 13.6 $J_{3ax,4ax}$ = 10.3 $J_{3ax,4eq}$ = 3.4	$J_{3eq,4eq}$ = 5.6 $J_{3eq,4ax}$ = 2.0 $J_{3eq,5eq}$ = 2.0	$J_{4ax,eq}$ = 12.8	$J_{4eq,6eq}$ = 1.3
6					
δ	3.45	3.08	2.93		
J_{HH}(Hz)	$J_{2,3ax}$ = 7.7 $J_{2,3eq}$ = 5.0 $J_{2,6ax}$ = 1.4	$J_{3ax,eq}$ = 11.6 $J_{3ax,5ax}$ = 1.3	$J_{3eq,5eq}$ = 1.6		

5	H-5$_{ax}$	H-5$_{eq}$	H-6$_{ax}$	H-6$_{eq}$	CH_2 CH$_3$	CH$_2$ CH_3
δ	1.21	1.31	1.81	2.19	4.01	0.98
J_{HH}(Hz)	$J_{5ax,eq}$ = 13.2 $J_{5ax,6ax}$ = 10.7 $J_{5ax,6eq}$ = 5.0	$J_{5eq,6ax}$ = 5.6 $J_{5eq,6eq}$ = 5.0	$J_{6ax,eq}$ = 13.6		J = 7.2	J = 7.2
6						
δ	2.76	2.82	2.54	2.64	4.22	1.26
J_{HH}(Hz)	$J_{5ax,eq}$ = 11.3 $J_{5ax,6ax}$ = 8.0 $J_{5ax,6eq}$ = 4.8	$J_{5eq,6eq}$ = 6.5 $J_{5eq,6ax}$ = 5.5	$J_{6ax,eq}$ = 13.6		J = 7.2 Bz: 3.64 Ph: 7.19–7.31	J = 7.2

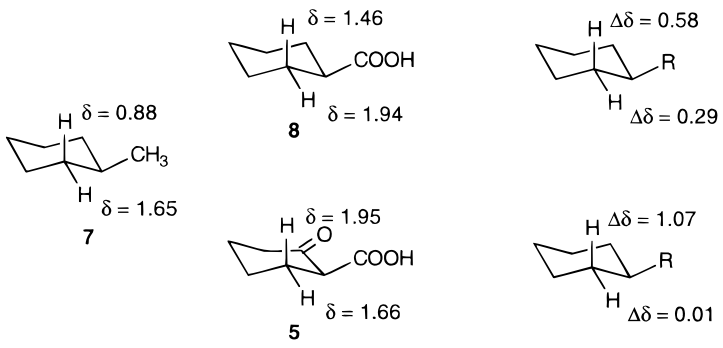
[a] Ketone : enol = 20 : 80 (benzene-d_6 solution), 40 : 60 (CDCl$_3$ solution).
[b] Ketone : enol = 38 : 62 (CDCl$_3$ solution).
[c] For better comparability, corresponding positions in **5** and **6** are numbered equally (Scheme 1).

tional search, which show that conformers with an equatorial carboethoxy substituent account for *ca.* 80% of the population (using the MM+ force field in Hyperchem 4.0[16]). Small four-bound couplings between protons assigned to occupy axial positions indicate the presence of further conformers in solution.

The source of the reversed chemical shift order of methylene protons in compounds **1a–c**, **5** and **6** and in part alcohols **4a** and **b**, is not immediately obvious. It has previously been speculated whether variations of $\Delta\delta_{eq,ax}$ in piperidone derivatives could be a result of the spatial arrangement of the nitrogen lone pair, with a shift to higher frequencies for protons *syn* to it.[8a,17] This possibility has been rejected by others,[18] and can also be discarded in the present case.

It is tempting to assume that a change in electron density of the bonds between C-1/C-5 and C-9 causes the different chemical shift order for compounds **1a–c**, since the anisotropic shielding by these bonds is primarily responsible for the chemical shift difference of axial and equatorial methylene protons.[1] However, calculations did not provide any support, such as a pattern of bond orders, electron densities or molecular geometries, for this hypothesis (the semi-empirical methods AM1 and PM3 as implemented in MOPAC 6.0 were used).[19]

The anisotropy of the carboxyl ester substituent might be another source of the observed chemical shift changes. We therefore consider the methylene proton chemical shifts in the cyclohexane derivatives of Scheme 2, and in the bispidine derivatives with either CH$_3$ or COOCH$_3$ in positions 1 and 5 ($\Delta\delta H_{ax}$ and $\Delta\delta H_{eq}$, Table 4). Obviously, the carboxyl ester group increases the chemical shifts of the axial protons more than that of the equatorial protons, especially with a keto group in the β-position, which might influence its orientation.



Scheme 2.

If there were free rotation, equally large chemical shift increases for both axial and equatorial protons would be expected, which is not observed.

EXPERIMENTAL

Spectra

Spectra were measured on a Varian Unity instrument at 25 °C on solutions in $CDCl_3$ at 400 MHz for ^1H and 100 MHz for ^{13}C, respectively. Chemical shifts are indirectly referenced to TMS via the solvent signals (^1H, residual $CHCl_3$ at 7.26 ppm; ^{13}C, $CDCl_3$ at 77.0 ppm). Signal assignments were derived from HSQC,[13] HSBC,[20] P.E.COSY[21] and NOE difference[22] spectra. Heteronuclear Overhauser effect difference spectra[23] were obtained on non-degassed samples of 100–200 mg by selectively saturating the signal of the respective ^{12}C-bound proton for 30 s, followed by acquisition of the ^{13}C NMR spectrum with Waltz-16 proton decoupling, acquisition time 1.2 s, 384 transients and experiment time 3 h 20 min. A reference spectrum was obtained with the decoupler set off-resonance.

Materials

Bispidinone derivatives (Scheme 1) were prepared by a Mannich reaction from the corresponding acyclic ketones and benzylamine or aniline;[6b] **3a**, **3b** and **6** were prepared as described in the literature.[5a,c] Complete NMR data are given in Table 3. Compounds **5**, **7** and **8** were commercially available and used without further purification. Alcohols **4a–d** were prepared by reduction of the corresponding bispidinones (0.5 mmol) with $NaBH_4$ in THF–water (1:1) (5 ml). The reaction mixture was stirred for 1 h at room temperature, then cooled on an ice-bath and the pH was adjusted to *ca.* 1 with 50% aqueous HCl. Stirring was continued for an additional 30 min at room temperature. The reaction mixture was transferred to a separation funnel and the pH was adjusted to *ca.* 10 with 20% aqueous NaOH. This solution was extracted with chloroform (2 × 20 ml) and the combined organic phases were washed with water (50 ml). After evaporation, the remaining material was recrystallized from diethyl ether at − 20 °C. The colorless crystals were collected and dried *in vacuo*. **4a**: yield 34%; m.p. 100–104 °C; IR (KBr), 3488, 1734, 1721, 1260 cm^{-1}; MS, *m/z* 410 (M^+, 100%), 258, 105, 77; analysis, calculated for $C_{23}H_{26}N_2O_5$, C 67.34, H 6.34; found, C 66.45, H 6.31%. **4b**: yield 80%; m.p. 122 °C; IR (KBr), 3278, 2833, 1332, 1124 cm^{-1}; MS, *m/z* 438 (M^+, 10.4%), 347, 302, 134, 91; analysis, calculated for $C_{25}H_{30}N_2O_5$, C 68.51, H 6.84; found, C 68.39, H 6.86%. **4c**: yield 72%; m.p. 112–113 °C; ^{13}C NMR ($CDCl_3$), δ 138.9, 137.9, 128.6, 128.5, 128.2, 128.0, 126.9, 126.7, 81.0, 65.0, 61.8, 61.7, 59.4, 36.6, 23.7 ppm; IR (KBr), 3354, 2948, 2929, 2868, 2801, 1494. 1453 cm^{-1}; MS, *m/z* 350 (M^+, 10%), 259, 198, 91; analysis, calculated for $C_{23}H_{30}N_2O$, C 78.82, H 8.63; found, C 78.61, H 8.72%. **4d**: yield, 22%; m.p. 97 °C; ^{13}C NMR ($CDCl_3$), δ 150.3 (2C), 128.9 (2C), 118.3, 117.7, 114.9, 114.3, 77.9, 60.7, 53.2, 36.4, 22.4 ppm; IR ($CDCl_3$ solution), 3064, 2253, 1598, 1503, 1464 cm^{-1}; MS, *m/z* 322 (M^+, 10%), 184, 120, 106; analysis, calculated for $C_{21}H_{26}N_2O$, C 78.22, H 8.13; found, C 78.39, H 8.83%.

Methylcyclohexane **7**: ^1H NMR ($CDCl_3$), δ 1.68 (m, 2H, H-3_{eq}), 1.65 (m, 2H, H-2_{eq}), 1.62 (m, 1H, H-4_{eq}), 1.34 (m, 1H, H-1_{ax}), 1.23 (m, 2H, H-3_{ax}), 1.14 (m, 1H, H-4_{ax}), 0.88 (m, 2H, H2_{ax}), 0.86 (d, J = 6.5 Hz, CH_3). Cyclohexane carboxylic acid **8**: ^1H NMR ($CDCl_3$), δ 2.34 (tt, J = 3.7, 11.2 Hz, 1H, H-1), 1.94 (m, 2H, H-2_{ax}), 1.77 (m, 2H, H-3_{eq}), 1.65 (m, 1H, H-4_{eq}), 1.46 (m, 2H, H-2_{ax}), 1.30 (m, 2H, H-3_{ax}), 1.25 (m, 1H, H-4_{ax}).

Acknowledgements

We thank Professor R. Freeman for supplying us with the source code for his *J*-doubling routine. The Swedish Natural Science Research Council and Magn. Bergvalls Stiftelse are acknowledged for financial support.

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